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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/757,688	01/11/2001	Wolfgang Heil	PLOVIN-2A	7991

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1611	

NOTIFICATION DATE	DELIVERY MODE
06/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	09/757,688	HEIL ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *173-192,195-230,233 and 234* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *173-192,195-230,233 and 234* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2-23-09, 3-23-09, 11-26-08; 3-23-09 and 5-15-09 (total 5 IDS- 19 pages).

DETAILED ACTION

Receipt of response of 2-23-09 and IDS dated 2-23-09, 3-23-09, 11-26-08 and 5-15-09 is acknowledged.

In response to the District Court Decision holding claims of cited patent 6,787,531 obvious, the double patenting rejection of record is moot.

However, in view of the proceedings of District Court Decision of 3-3-2008 and the IDS filed by applicants, the following new rejection is applied:

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 173-192, 195-230, 233 and 234 are rejected under 35 U.S.C. 103(a) as being unpatentable Lignieres et al (hereafter Lignieres) in view of Furhmann et al (Furhmann).

3. Alternatively Claims 173-192, 195-230, 233 and 234 are rejected under 35 U.S.C. 103(a) as being unpatentable Lignieres et al (hereafter Lignieres) in view of Furhmann et al (Furhmann), and further in view of Hargrove (Absorption of oral progesterone is influenced by vehicle and particle size. American Journal of Obstetrics & Gynecology, v.161, no. 4, 1989, p 948-951), Aulton (Pharmaceutics, Science of dosage form designs), **Krause I** (Krause et al., Determination of Plasma Levels of

Spirenone, a New Aldosterone Antagonist, and One o fits Metabolites by High-Performance Liquid Chromatography, Journal of Chromatography, 230 (1982) 37-45) and **Krause II** (Krause et al, Isolation and Identification of Spirenone Metabolites from the Monkey (Macaca Fascieularis), Steroids, vol. 40, No. 1, pp. 81-90, July 1982).

4. Lignieres et al and Furhmann et al have been used to reject instant claims in the action dated 4-5-04.

5. Lignieres teaches administering a combination of estrogen and micronized progesterone for postmenopausal estrogen/progestin intervention so as to protect pre- and postmenopausal women from endometrial hyperplasia (abstract, page 47, col. 1). Lingnieres suggests administering micronized progesterone for about 10 days during second half of menstrual cycle, so as to effectively prevent endometrial hyperplasia (page 51). Examiner notes that instant claims also administer drospirenone, a progestogen, in the second half of the cycle. Lingniere suggests that micronization &progesterone substantially increased the bioavailability &the hormone and oral administration of micronized progesterone has been shown to be very effective for controlling endometrial growth (page 42, col. 2). Lingniere suggests progesterone and also estradiol (page 48, col. 2), but not DSRP as claimed.

6. Furhmann teaches drospirenone a progestin that is structurally related to spironolactone but functionally having similar pharmacological profile to progesterone. Furhmann teaches that DSRP exhibited a high binding affinity to progesterone receptor

and similar to progesterone showed a low affinity to the androgen receptors and a high affinity to mineral corticoid receptors (page 247). Furhmann also suggests that DSRP exhibits an anti-androgen activity that is five to ten times higher than progesterone (page 248), which is attributed to the higher metabolic stability of DSRP as compared to that of progesterone (page 249, col. 1). It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use drospirenone of Furhmann in combination with estradiol for treating endometrial hyperplasia and thus protecting endometrium in postmenopausal women because Fuhrmann teaches drospirenone is a synthetic progestin that shows a similar pharmacological profile as that of natural progesterone and higher stability than progesterone. Further, while Fuhrman does not suggest micronized DSRP, Lignieres suggests micronization of progesterone for increased bioavailability upon oral administration, as high as 50% to 60%. Lignieres also suggests that while different progesterones induce different bleeding patterns, oral progesterone induces significantly less bleeding (last line of page 51). Accordingly, one of an ordinary skill in the art would have expected that DSRP of Fuhrmann that is similar in activity to progesterone also exhibit the same high efficacy in inhibiting endometrial bleeding. Further, one of an ordinary skill in the art would have expected that upon micronization of DSP the bioavailability is increased, and as a result of micronization gastrointestinal absorption is rapid, which increases the amount of surface area of the steroid that comes in to contact with the mucous membranes (paragraph connecting 53-54). Lingnieres suggests several dosing schedules for estrogen and progesterone. Accordingly, optimizing the amounts and dosages of

hormones of WO, depending on the duration of administration, with an expectation to provide maximum therapeutic effect would have been obvious for one of an ordinary skill in the art. With respect to the claimed amounts of estrogen and DSRP, Lignieres suggest the effective dosages for treating endometrial hyperplasia and one of an ordinary skill in the art would have extrapolated the dosages of progesterone to DSRP for the reasons that both progesterone and DSRP exhibit same pharmacological activity. Further, in the absence of any criticality established, choosing the particle size of DSRP by routine experimentation with an expectation achieve optimum bioavailability would have been obvious for a skilled artisan. With respect to the claimed method of treating symptoms, disorders, diseases associated with deficient endogenous levels of estrogen, Lignieres suggests endometrial hyperplasia and other postmenopausal symptoms that are within the scope of claimed symptoms, diseases etc. Further, preparing an oral pharmaceutical dosage form such as a tablet comprising estrogen, micronized DSRP and the conventional pharmacological excipients would have been within the scope of a skilled artisan because Lignieres suggests that oral administration of estrogen/progestin is effective than transdermal or intravenous.

Examiner notes that a rejection over Lignieres and Furhmann has been withdrawn in view of the declaration of Lipp, discussed in the interview of 11-10-04. However, in view of the findings of the District Court (submitted by applicants) and the detailed explanation therein rendering the micronization of drospirenone as being obvious, the above references are reinstated. The following excerpts from the Court findings have been used to explain the teachings of Hargrove et al, Aulton, Krause I and Krause II.

On page 40 of the decision, it is explained that Aulton discusses the correlation between in vitro and in vivo studies. Page 42 onwards, the Decision discusses the importance of micronization

"Drospirenone is a poorly water soluble steroid (7T 4, 9-10; 7T 63, 20-24). Reducing particle size increases the rate of dissolution, causing more of the drag to be absorbed in the body (1T 40, 6-19; 7T 63, 4-6). The first step when formulating a poorly water soluble drug is to micronize the drug in order to improve its dissolution rate (IT 40, 6-8; 5T 20, 16-21; 7T 65, 23 through 66, 3). Dr, Chambliss contends that the prior art bears out this rule even with regard to drugs related to drospirenone (1T 44, 11-24). Citing to McInnes (JX 019), 14 Chambliss testified that micronization of spironolactone (Def. 20 at p, 7) led to improved bioavailability (IT 45, 3 through 48, 25).

Aulton recognizes that one of the chief techniques a formulator uses to increase bioavailability of a poorly water soluble drug like drospirenone is the particle's size. Altering particle size is a means for overcoming drug limitations (PTX 19 at 7), By micronizing, there is n increase in surface area which leads to increased dissolution and improved absorption. Aulton emphasizes: Particle size reduction results in an increase in the specific surface (i.e. surface area per unit weight of powders). Drug dissolution rate, absorption rate, dosage form content uniformity and stability are all dependent to varying degrees on particle size, size distribution and interactions of solid surfaces. In many cases for both drugs and additives particle size reduction is required to achieve the desired physicochemical characteristics. It is now generally recognized that poorly soluble drugs showing a dissolution rate limiting step in the absorption process wilt be

more readily bioavailable when administered in a finely subdivided form with larger surfaces than as the coarse material .... The fine material often in micronized form with larger specific surface dissolves at faster rates which can lead to improved drug absorption by passive diffusion. Although the general rule is that micronizing increases dissolution rate, it is not always the case because the drug may become more unstable - "reduced chemical stability." (PTX 19 at 8), Sometimes extensive particle size reduction increases "the tendency of the particles to aggregate" which would decrease bioavailability. Aulton recognizes the uncertainty of reducing particle size of acid sensitive drugs. Thus, chemical degradation will be minimized if an acid-unstable drug does not dissolve readily in gastric fluids; or stated differently, micronization may increase the extent of drug degradation. This would result in a decrease in the amount of intact drug available for absorption (PTX 19 at 156). Despite the warning about acid-sensitive drugs, Aulton also notes that there are exceptions to the role like digoxin and spironolactone (IT 58, 3-14; PTX 19 at 156).~5 In addition to Aulton, there are a number of references to prior art concerning micronization of poorly water soluble drugs. They are reviewed below. One of those poorly water soluble sex steroids on which micronization assists in dissolution is progesterone.

District court also refers to Hargrove article and states:

In the Hargrove article, the author sets out to determine whether particle size and vehicle (dosage form) could improve intestinal absorption of progesterone in order to increase its bioavailability. Previously, oral dose form of progesterone had proven ineffective. Hargrove used five different dosage forms including plain milled, micronized,

and enteric coated progesterone. Six postmenopausal women and one man volunteered. Each subject was tested six times. Hargrove found that the optimal preparation for oral administration of natural progesterone is "micronization of the particles and dissolution in oils." He further found that the process of enteric coating to protect against gastric acidity did not increase absorption (DX 42 at 951). Hargrove teaches that "absorption of oral progesterone is influenced by vehicle and particle size; that "[m]icronized progesterone, in oil showed the highest average progesterone concentration.., and the shortest time from ingestion to measured peak." (DX 42 at 948-949). Although the study does not specifically address drospirenone, it confirms that not all acid-sensitive drugs require enteric coating.

The Court concludes, and the experts agree that the prior art generally instructs that micronization may improve the dissolution of drospirenone (IT 40, 6-8; 5T 20, 1.6-21; and 7T 65, 23 through 66, 3). Undoubtedly, there would be some concern about dissolution of a poorly water soluble acid sensitive drug, but the person of ordinary skill in the art would conclude that micronization is a viable option.

The court also concludes that based on Aulton's teachings, inter- and intra- subject variability is a major disadvantage, and therefore the contention that the person of ordinary skill in the art would automatically be directed to enteric coat drospirenone is rejected (page 50 of the decision). The person of ordinary skill in the art would not rule out formulating a micronized drospirenone without enteric coating in order to overcome variability concerns.

According to the evidence submitted by Krause I, court finds that Krause teaches that lactone rearrangement product of spirenone [the isomer] was not detectable in the plasma, suggesting that the absorption process may be faster than the acid catalyzed isomerization of the drug." Further, Krause II *also failed to find any isomers in blood plasma. Thus, the court finds that the drug drospirenone is absorbed in vivo, even though it is isomerize in vitro.*

Even though Krause studied spirenone, it is related to drospirenone because of the evidence :

1. drospirenone and spirenone are both acid sensitive, and isomerize at similar rates in vitro (7T 112, 7; 3T 144, 24 through 145, 1; 1T 71, 19-23);

2. both are steroids (7T 112, 5);

3. drospirenone and spirenone are derivatives of spirolactone (7T 111, 10-11);

4. both have same chemical structure but for one chemical bond at one location;

5. the steroids have the same pharmacological properties (7T 115, 15-25); and

The Court concludes that the person of ordinary skill in the art would find the drugs are closely related (about as close as fraternal twins) and would assess these studies when formulating drospirenone.

Thus, it would have been obvious for one of an ordinary skill in the art micronization is a common technique to increase absorption or bioavailability (this is the same rationale that examiner used in combining the teachings of Lignieres and Furhmann), and

Hargrove teaches poorly soluble sex steroids benefit from micronization (see page 70 of the Court decision)

. ***Double Patenting***

1. Claims 173-192, 195-230, 233 and 234 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-49 of U.S. Patent No. 6869941 in view of Furhmann and Lignieres or in view of Furhmann, Lignieres, Krause I, Krause II, Hargrove et al and Aulton.

Although the method of treating a disease, disorder or symptom issued in the above patent is broader in scope than the instant method claims, the issued claims are overlapping in scope with that of the instant claims because the dosage regimen of estrogen and drospirenone of the issued claims follow the same pattern as that of the instant regimen to achieve the claimed method. By definition, the effective amount of drospirenone for achieving the above regimen (and hence the method) of the issued claims involves micronized drospirenone having the same surface area and particle sizes as that of the instant claims and also has the same dissolution pattern as claimed in the instant application. Thus, the method of the patented as well as the instant claims involves the same composition and hence the instant method would have been obvious for one of an ordinary skill in the art at the time of the instant invention from the patented claims.

Further, the above rejection is substantiated by the teachings of Furhmann, Lignieres, Krause I, Krause II, Hargrove et al and Aulton and the decisions rendered by

District Court, all of which have been explained in detail in the preceding section. It was clearly established that micronization of drospirenone to increase bioavailability would have been within the scope of a skilled artisan.

2. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611
June 8, 2009